Early goal-directed therapy reduced mortality and multiorgan dysfunction in severe sepsis or septic shock

Rivers E, Nguyen B, Havstad S, et al., for the Early Goal-Directed Therapy Collaborative Group. **Early goal-directed therapy in the treatment of severe sepsis and septic shock.** N Engl J Med. 2001 Nov 8;345:1368-77.

QUESTION

In patients with severe sepsis or septic shock, does early goal-directed therapy (EGDT) before admission to the intensive-care unit (ICU) reduce mortality and multiorgan dysfunction?

DESIGN

Randomized {allocation concealed*}†, blinded (clinicians),* controlled trial with 60-day follow-up.

SETTING

Emergency department (ED) of a U.S. academic tertiary-care hospital.

PATIENTS

263 adults (mean age 66 y, 51% men) who met 2 of 4 criteria for the systemic inflammatory response syndrome (based on temperature, leukocyte count, tachycardia, and hyperventilation) and had systolic blood pressure ≥ 90 mm Hg (after crystalloid-fluid challenge of 20 to 30 mL/kg of body weight over 30 min) or a blood lactate level ≥ 4 mmol/L. Exclusion criteria included mostly the presence of such acute disorders as seizure, stroke, status asthmaticus, or burn. Follow-up was 100%.

INTERVENTION

Patients were allocated to EGDT for ≥ 6 hours (n = 130) or to standard therapy in the ED (n = 133). All patients received a central venous catheter; however, patients in the EGDT group received a central venous catheter capable of continuously monitoring venous oxygen saturation (VOS). Both groups received a 500-mL bolus of crystalloid every 30 minutes to achieve a central venous pressure (CVP) of 8 to 12 mm Hg. Vasopressors were given if the mean arterial pressure (MAP) was < 65 mm Hg, and vasodilators were given if the MAP was > 90 mm Hg. In the EGDT group, if central VOS was < 70%, erythrocytes were transfused to achieve a hematocrit of ≥ 30%; if central VOS was still < 70%, dobutamine was given (2.5 µg/kg per min and titrated every 30 min up to 20 µg/kg per min unless the MAP was < 65 mm Hg or the heart rate was > 120 beats/min).

MAIN OUTCOME MEASURES

In-hospital death. Secondary outcomes included death and organ-dysfunction scores (24-point Multiple Organ Dysfunction score).

MAIN RESULTS

Analysis was by intention to treat. During the first 6 hours of treatment, both groups met the goals for CVP and MAP, although the control group received less fluid (mean 3.5 vs 5.0 L) and fewer blood transfusions (19% vs 64%). Later, in the ICU, the control group received more fluid, erythrocyte transfusions, vasopressors, mechanical ventilation, and pulmonary-artery catheterization. Fewer patients in the EGDT group than in the standard-therapy group died in the hospital (P = 0.009) or by 60 days (P = 0.03) (Table). Organ dysfunction scores were lower in the EGDT group than in the standard-therapy group (P < 0.001) (mean score difference 0.9, 95% CI 0.0 to 1.8 at 6 h; 1.3, CI 0.3 to 2.3 at 7 to 72 h).

CONCLUSIONS

In patients with severe sepsis or septic shock, early goal-directed therapy reduced mortality and organ dysfunction.

Sources of funding: Henry Ford Health Systems Fund for Research; Weatherby Healthcare Resuscitation Fellowship; Edwards Lifesciences; Nova Biomedical.

For correspondence: Dr. E. Rivers, Henry Ford Hospital, Detroit, MI, USA. E-mail erivers1@hfhs.org.

*See Glossary.

†Information provided by author.

Early goal-directed therapy (EGDT) vs standard therapy for severe sepsis or septic shock‡

Outcomes	EGDT	Standard therapy	RRR (95% CI)	NNT (CI)
In-hospital mortality	31%	47%	42% (13 to 62)	6 (4 to 17)
Mortality at 60 d	44%	57%	33% (4 to 54)	86 (4 to 44)

‡Abbreviations defined in Glossary; NNT and CI calculated from data in article.

COMMENTARY

The study by Rivers and colleagues provides important support for rapidly and fully resuscitating patients with severe sepsis or septic shock. The EGDT group received multiple protocol-driven interventions triggered by frequently monitored physiologic measurements. However, understanding the care provided to the control group is essential for applying these results clinically. During unblinded treatment in the ED, the same hemodynamic goals of CVP between 8 and 12 mm Hg and of MAP between 65 and 90 mm Hg were used to trigger fluid boluses and vasopressor therapy in both groups, but the control group received less fluid. Consistent with this treatment difference, CVP and MAP were both lower in the control group at 6 hours. Furthermore, 18 of 133 patients in the control group but only 1 of 130 patients in the EGDT group did not reach the combined physiologic end points for CVP, mean arterial blood pressure, and urine output of at least 0.5 mL/kg per hour (P < 0.001). Later, in the ICU, the control group received more fluid than did the EGDT group, but the adverse effect on survival of early deficiencies could not be overcome.

Death attributable to sudden cardiovascular collapse but not to multiple organ failure occurred less frequently in the EGDT group. Because of several treatment differences between study groups, it cannot be determined which aspect of the protocol was most crucial in producing this observed effect on survival. Moreover, large beneficial effects of some interventions, such as better fluid resuscitation, could have obscured harmful effects of others. A point not addressed but of equal importance to rapid resuscitation is the need to start antibiotics within 60 minutes of diagnosing severe sepsis. Approximately 6 hours after randomization for severe sepsis or septic shock, 1 in 10 patients in this study had not received antibiotics. Clearly, septic patients are best served by promptly initiating antimicrobial therapy and rapid life-saving resuscitation based on frequent physiologic measurements.

Charles Natanson, MD
Robert L. Danner, MD
National Institutes of Health
Bethesda, Maryland, USA